



Attorney Docket No. 5405.223IPDV

PATENT

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:                   Opara   Group Art Unit: 1651  
Serial No.:       10/054,796                                   Examiner: D. Naff  
Filed:             January 23, 2002  
For:               *METHODS OF ENCAPSULATING CELLS*

September 16, 2003

Commissioner for Patents  
Post Office Box 1450  
Alexandria, Virginia 22313-1450

Response to Official Action

This is in response to the Official Action of July 1, 2003.

## CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Post Office Box 1450, Alexandria, Virginia 22313-1450, on September 16, 2003.

*Vickie Diane Prior*  
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Date of Signature: September 16, 2003

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This is in response to the Official Action of July 1, 2003. The points raised therein are addressed below in the order originally set forth.

**1. The prior art rejection.**

Claims 6–13, 77 and 84 stand rejected as obvious under 35 USC 103(a) over:

(a) **Brothers**, in view of

(c) **Brockbank** or **Hamaguchi et al.** or **Garfinkel et al.**, each taken with

(c) **Janjic et al.** or **Littman et al.** or **Garfinkel et al.**

For the reasons set forth below, this rejection is respectfully traversed.

The Official Action asserts that it would have been obvious to carry out the encapsulation of pancreatic islet cells as suggested by **Brothers** (U.S. Patent No. 5,821,121) by microencapsulating the cells to obtain the function of microencapsulating the pancreatic islets for transplantation as taught by **Brockbank**, (U.S. Patent No. 5,071,741) **Hamaguchi et al.** (*Diabetes Res. Clin. Pract.* 2:337–345 (1986)) or **Garfinkel et al.** (*J. Surg. Res.* 76:7–10 (1998)) when microencapsulating pancreatic islets for transplantation. **Janjic et al.** (*Pancreas* 13:166–172 (1996)), **Littman et al.** (*J. Surg. Res.* 59:694–698 (1995)) or **Garfinkel et al.** (*FASEB J. H*:A436 #2520 (1997))) would have suggested that glutathione in the medium of **Brothers** will function to enhance insulin secretion by the pancreatic islets. It is alleged that the resulting cultured microencapsulated cells would have inherently had a weight gain and basal insulin secretion as presently claimed. As explained in greater detail below, the cited reference do not in fact disclose products that have possess the features recited in the instant claims or make obvious how such features could be obtained. Accordingly, this rejection is respectfully traversed.

**Brothers** discloses methods for establishing and maintaining pancreatic islet cells in long term cell culture in a medium containing glutathione and suggests that these cells may be encapsulated for implantation.

**Brockbank** discloses a novel class of nonpermeating cryoprotectants which, when mixed with certain known permeating cryoprotectants, provide a medium for protection of living cells during a cryopreservation process. **Hamaguchi et al.** discloses a technique for microencapsulating pancreatic islet cells and its application

to culture and transplantation. Garfinkel et al. (1998) discloses that the chelation of microencapsulated islets with, for example, sodium citrate appears to be essential for optimal function (insulin secretion upon glucose challenge) of said islets.

**Janjic et al.** discloses that the glutathione redox state (GSH/GSSG) in human islet cells decreases after crypreservation and that insulin secretion of cryopreserved human islet cells can be improved by treatment with antioxidants (BHA). **Littman et al.** discloses that incubating of isolated islets with glutathione preserved and enhanced islet function. Finally, **Garfinkel et al.** (1997) discloses that porcine islets that are pre-treated with glutathione enhance pancreatic islet function in vitro.

The present claims are drawn to a microencapsulated cell product containing microcapsules containing pancreatic islet cells treated during manufacture with a physiologically acceptable salt to increase microcapsule durability, wherein the cells exhibit a weight gain of not more than 10 percent over a period of one month in a physiological saline solution at 37 °C and exhibiting at least 150% basal insulin secretion in response to 16.7 mM glucose challenge in Krebs-Ringer physiological solution at pH 7.4 after a period of one month. The salt treatment is recited in claims 85 and 86, which generally correspond to language found in originally presented claim 62 in product-by-process form.

Although insulin secretion in response to glucose challenge has been characterized to an extent in the references cited in the Official Action, treatment of microencapsulated islets with a physiologically acceptable salt such as sodium sulfate as is claimed in the present invention is not disclosed in the cited references. Without such treatment the product would not achieve the performance characteristics recited in the instant claims. Furthermore, Applicant believes that there is no indication that cellular weight gain was characterized, let alone present to the extent as claimed in the present invention in conjunction with an increase in insulin secretion in response to glucose.

It is stated in § 2112 of the MPEP that the Examiner must provide rationale or show evidence tending to show inherency. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) states that:

“To establish inherency, the extrinsic evidence ‘must make clear that the missing descriptive matter is necessarily present in the thing

described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probability or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.”

Applicant respectfully disagrees with the assertion in the Official Action that a microencapsulated cell product prepared according to the teachings of above-mentioned references would have inherently had a weight gain and basal insulin secretion as is claimed in the present application. The Official Action provides no support for the assertion that a microencapsulated cell product prepared according to the teachings of the cited references would inherently have a weight gain and basal insulin secretion as is claimed in the present invention.

One of the concerns with polylysine alginate microencapsulated cells is their durability, in particular with microcapsules that have been chelated (Lines 11–13, second paragraph of the introduction, Garfinkel et al. (1998) *J. Surg. Res.* 76:7–10, document 266 on 1449). Furthermore, the concerns of the long-term durability of microencapsulated islets are related in part to bead swelling, which results in disintegration of capsules due to colloid osmotic pressure induced by residual  $\text{Ca}^{++}$  after chelation of the microcapsules with sodium citrate in a manner as taught by Garfinkel et al. (1998) and discussed in Kendall et al. (2000) *Curr. Surg.* 57:636–637, first paragraph. **Microcapsules prepared in this manner increased in diameter by 20% in 9 days, followed by disintegration or became nonspherical. Thus microencapsulated cells and products thereof do not inherently have the characteristics of weight gain and basal insulin secretion of the present invention.** However, no significant increase in size for up to 34 days was observed in microcapsules that are subsequently incubated with a physiologically acceptable salt as is outlined in paragraph 44 of the present application, such as sodium sulfate and shown in Kendall et al (2000).

In view of the foregoing, Applicants believe that this rejection has been overcome and respectfully request its withdrawal.

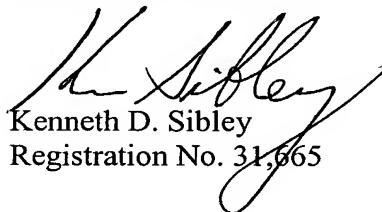
**2. The non-statutory double patenting rejection.**

Claims 6-13, 77 and 84 stand rejected for obviousness-type double patenting over claims 1-15 of US Patent No. 6,303,355. Claims 1-15 in the cited patent correspond to claims 14-28 of the application. In the application upon which the cited patent was based, a restriction requirement was issued in which group I contained claims 1-13 and 30-61, while group II contained claims 14-29. Group II was elected and the claims to group I were cancelled. A copy of said restriction requirement is enclosed. As the present claims correspond to the cancelled group I and not elected group II, it is respectfully submitted that the now issued patent is not available as a double patenting reference against the claims currently presented in the instant application, and it is respectfully submitted that this rejection should now be withdrawn.

If the foregoing arguments are deemed unpersuasive by the examiner and the obviousness rejection is deemed overcome by the arguments set forth above, so that the submission of a terminal disclaimer is the only remaining issue in the case, the examiner is requested to contact applicants undersigned representative by phone so that a terminal disclaimer may be submitted to moot this issue and this case can be expeditiously passed to allowance.

Applicant believes that no fee is due. However, the Commissioner is hereby authorized to charge any deficiency to Deposit Account No. 50-0220.

Respectfully submitted,

  
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